Poster LB010

First-line trastuzumab deruxtecan regimens in advanced HER2-positive gastric cancer, gastroesophageal junction adenocarcinoma, or esophageal adenocarcinoma: exploratory analysis of baseline HER2-related biomarkers in DESTINY-Gastric03 Part 2

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Objective

- To present the DESTINY-Gastric03 (NCT04379596) Part 2 exploratory analysis, evaluating baseline human epidermal growth factor receptor 2 (HER2)–related biomarkers in advanced HER2-positive (HER2+; immunohistochemistry [IHC] 3+ or IHC 2+/in situ hybridization–positive [ISH+]) gastric cancer (GC), gastroesophageal junction adenocarcinoma (GEJA), or esophageal adenocarcinoma (EA) treated with first-line trastuzumab deruxtecan (T-DXd)–based regimens

Conclusions

- Agreement (80.4%) between HER2 IHC results by local testing with HER2 positivity (IHC 3+ or IHC 2+ / ISH+) and by central testing was broadly consistent with prior studies in GC[1,2]
- HER2+ expression by IHC/ISH and tumor or plasma *HER2* (*ERBB2*) amplification were generally associated with higher objective response rates (ORRs) for patients with HER2+ GC, GEJA, or EA who received first-line T-DXd-based regimens, versus those with HER2− expression by IHC/ISH and/or without amplified *HER2*
  - Trends of longer progression-free survival (PFS) were generally observed for patients with tumor- or plasma-amplified *HER2* versus those without amplification within most treatment arms; however, interpretation was limited by sample sizes
- Data provide further evidence of antitumor activity for first-line T-DXd-based combinations in advanced HER2+ GC, GEJA, or EA

Plain language summary

Why did we perform this research?
Human epidermal growth factor receptor 2 (HER2) is a protein found at high levels in some cancers (known as HER2-positive or HER2+), including those in the stomach (gastric cancer [GC]), where the stomach meets the food pipe (gastroesophageal junction adenocarcinoma [GEJA]), and in the food pipe (esophageal adenocarcinoma [EA]).[1–3] Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate, which is a chemotherapy with a linker (together called deruxtecan) joined to an antibody (trastuzumab). T-DXd binds to HER2 on the surface of cancer cells. Once inside the cell, it releases the chemotherapy to kill these cells.[4,5] T-DXd is approved in multiple countries for people with previously treated HER2+ GC or GEJA that has spread from its original site to other parts of the body (known as advanced or metastatic cancer).[6,7] Initial results from Part 2 of the DESTINY-Gastric03 study showed that T-DXd alone or combined with chemotherapy and/or pembrolizumab (a cancer drug that targets a protein called programmed cell death protein 1) decreased the size or number of selected tumors (known as an objective response) in people with HER2+ GC, GEJA, or EA who had not received any prior treatment for advanced or metastatic disease.[8,9] Studying how different HER2 characteristics impact response to T-DXd-based treatment regimens may help to better understand which people are most likely to benefit from such treatment.

How did we perform this research?
In DESTINY-Gastric03 Part 2, participants with advanced GC, GEJA, or EA received either trastuzumab (HER2-targeting antibody) + chemotherapy, or T-DXd alone or in combination with chemotherapy and/or pembrolizumab. Participants had not received any prior treatment for advanced disease. This analysis evaluated treatment responses according to high or lower levels of HER2 (known as the immunohistochemistry [IHC] status) determined at local testing sites versus one specialized (central) HER2 testing site, which ensured consistent use of the same HER2 testing protocol for all samples. Treatment responses according to whether participants carried extra copies of the *HER2* (*ERBB2*) gene, determined by assessing DNA from participants' tumors (tumor DNA) or blood plasma (circulating tumor DNA), were also evaluated.

What were the findings of this research?
Overall, we found that participants with advanced GC, GEJA, or EA with elevated HER2 expression by IHC (per local or central testing) or extra copies of the HER2 gene had greater objective responses to T-DXd-based regimens, compared with those with lower HER2 expression by IHC (per local or central testing) and/or without extra copies of the *HER2* gene.

What are the implications of this research?
These results provide further evidence of the benefit of T-DXd-based treatment combinations for people with advanced or metastatic HER2+ GC, GEJA, or EA who have not received any prior treatment for advanced or metastatic disease.

Where can I access more information?
For more information about DESTINY-Gastric03, please visit https://clinicaltrials.gov/study/NCT04379596. You can also speak to your doctor about this and other clinical studies.

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Poster

This study was sponsored by AstraZeneca. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).
Poster presented at AACR 2026 by Dr Yelena Y Janjigian. Corresponding author email address: janjigiy@mskcc.org

Introduction

- Trastuzumab (a HER2-directed antibody) in combination with pembrolizumab (pembro; an anti-programmed cell death protein 1 antibody) and chemotherapy is approved as first-line treatment for advanced HER2+ (IHC 3+ or IHC 2+/ISH+) GCs with programmed cell death ligand 1 (PD-L1) combined positive score (CPS) ≥1[3,4]
- T-DXd (a HER2-directed antibody-drug conjugate) 6.4 mg/kg monotherapy is approved in multiple countries for locally advanced or metastatic HER2+ GC or GEJA after an indicated HER2-directed regimen[5,6]
- DESTINY-Gastric03 is a Phase 1b/2 multipart study evaluating T-DXd-based combinations in advanced HER2-expressing GC, GEJA, or EA[7]
  - Preliminary results from Part 2 (dose expansion) showed antitumor activity for first-line T-DXd alone and in combination with a fluoropyrimidine (FP; 5-fluorouracil or capecitabine) and/or pembro in advanced HER2+ GC, GEJA, or EA[8]
- An exploratory biomarker analysis of the Phase 2 DESTINY-Gastric01 study, evaluating T-DXd 6.4 mg/kg versus third- or later-line chemotherapy in advanced HER2+ GC or GEJA, showed that baseline HER2-associated biomarkers correlated with T-DXd antitumor activity[9]
- This poster explores the relationship between baseline HER2-associated biomarkers and clinical outcomes in patients from DESTINY-Gastric03 Part 2

Methods

- DESTINY-Gastric03 (NCT04379596) is a Phase 1b/2, open-label, multicenter, dose-escalation (Part 1) and -expansion (Parts 2, 3, 4, and 5) study[7]

Patient population: Part 2

- Adults (aged ≥18 years) with unresectable, locally advanced or metastatic HER2+ (IHC 3+ or IHC 2+/ISH+ per local assessment) GC, GEJA, or EA*
- Treatment naïve for advanced or metastatic disease
- Eastern Cooperative Oncology Group performance status of 0 or 1

Testing methods: exploratory analysis

- Concordance of baseline tumor and plasma *HER2* amplification with central HER2 IHC/ISH status (HER2+: HER2 IHC 3+ or IHC 2+/ISH+; HER2−: HER2 IHC 2+/ISH-negative (ISH−) or IHC 1+/0) was assessed according to positive percentage agreement (PPA) and negative percentage agreement (NPA)
- ORRs were reported by local and central HER2 IHC/ISH status (HercepTest for central IHC) and by plasma (GuardantOMNI) and tumor (FoundationOneCDx) *HER2* (*ERBB2*) amplification

Treatment arms: Part 2

- Trastuzumab + FP + cisplatin/oxaliplatin†
- T-DXd 6.4 mg/kg
- T-DXd 6.4 mg/kg‡ + FP§
- T-DXd 6.4 mg/kg‡ + FP§ + pembro*
- T-DXd 6.4 mg/kg + pembro*
- T-DXd 5.4 mg/kg + FP‡ + pembro*

Data cutoff

February 28, 2025

Endpoints

Primary:
- Confirmed ORR¶

Secondary:
- DOR¶
- DCR¶
- PFS¶
- OS
- Frequency of adverse events and serious adverse events

Exploratory:
- **Subgroup analyses by baseline HER2-associated biomarkers**

T-DXd: IV Q3W. Pembro: 200 mg IV Q3W. *Following the initiation of Part 2, the US Food and Drug Administration approved pembro with trastuzumab and chemotherapy in first-line HER2+ advanced GC/GEJA (PD-L1 CPS ≥1), and pembro with chemotherapy in first-line EA/GEJA (PD-L1 CPS ≥1); therefore, Part 2 was amended to include T-DXd-based arms with pembrolizumab and/or FP, and enrollment of patients with HER2+ EA.[4] †trastuzumab 8 mg/kg initial dose then 6 mg/kg IV Q3W, investigator choice of 5-FU 800 mg/m^2 continuous IV infusion, Days 1–5, Q3W, or capecitabine 1000 mg/m^2 orally, BID, Days 1–14, Q3W, and investigator choice of cisplatin 80 mg/m^2 IV, Q3W, or oxaliplatin 130 mg/m^2 IV, Q3W; ‡dose in combination with FP established in Part 1; §investigator choice of 5-FU 600 mg/m^2 continuous IV infusion, Days 1–5, Q3W, or capecitabine 1000 mg/m^2 orally, BID, Days 1–14, Q3W (dose established in Part 1); ¶investigator choice of 5-FU 600 mg/m^2 continuous IV, Days 1–5, Q3W, or capecitabine 750 mg/m^2 orally, BID, Days 1–14, Q3W; #investigator assessed per RECIST 1.1. 5-FU, 5-fluorouracil; BID, twice daily; CPS, combined positive score; DCR, disease control rate; DOR, duration of response; EA, esophageal adenocarcinoma; FP, fluoropyrimidine; GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2(+), human epidermal growth factor receptor 2(−positive); IV, intravenous; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand 1; pembro, pembrolizumab; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan

Results

- At data cutoff (February 28, 2025), 230 patients had been assigned treatment in Part 2; of these, 229 patients had received treatment across six arms
- Median (range) follow up per treatment arm was:
  - Trastuzumab + FP + cisplatin/oxaliplatin: 18.4 (1.3–53.7) months
  - T-DXd 6.4 mg/kg: 16.7 (0.4–46.9) months
  - T-DXd 6.4 mg/kg + FP: 21.3 (0.7–41.4) months
  - T-DXd 6.4 mg/kg + FP + pembro: 18.0 (0.4–33.2) months
  - T-DXd 6.4 mg/kg + pembro: 15.1 (1.3–33.4) months
  - T-DXd 5.4 mg/kg + FP + pembro: 12.9 (1.0–17.2) months
- Baseline demographics and clinical characteristics by treatment arm are summarized in **Table 1**
- Overall, 80.4% (n=160/199) of HER2+ (IHC 3+ or IHC 2+/ISH+) GCs, GEJAs, or EAs by local testing were centrally scored as HER2+ (**Table 2**)
- Of the GCs, GEJAs, and EAs scored as HER2 IHC 3+ and IHC 2+/ISH+ by local testing, 86.1% (n=143/166) and 51.5% (n=17/33) scored as HER2+ by central testing, respectively

Table 1. Baseline demographics and characteristics by treatment arm

	Trastuzumab + FP + cisplatin/ oxaliplatin n=29	T-DXd 6.4 mg/kg n=43	T-DXd 6.4 mg/kg + FP n=41	T-DXd 6.4 mg/kg + FP + pembro n=43	T-DXd 6.4 mg/kg + pembro n=41	T-DXd 5.4 mg/kg + FP + pembro n=32
Median age, years (range)	64 (31–83)	61 (41–85)	60 (27–82)	65 (41–80)	66 (33–81)	61 (20–78)
Sex, n (%)						
Female	10 (34.5)	13 (30.2)	10 (24.4)	10 (23.3)	8 (19.5)	3 (9.4)
ECOG PS, n (%)						
0	13 (44.8)	21 (48.8)	19 (46.3)	23 (53.5)	23 (56.1)	17 (53.1)
1	16 (55.2)	22 (51.2)	22 (53.7)	20 (46.5)	18 (43.9)	15 (46.9)
Primary tumor site, n (%)						
Esophagus	0	0	0	8 (18.6)	10 (24.4)	4 (12.5)
Stomach	23 (79.3)	29 (67.4)	22 (53.7)	27 (62.8)	25 (61.0)	21 (65.6)
GEJ	6 (20.7)	14 (32.6)	19 (46.3)	8 (18.6)	6 (14.6)	7 (21.9)
Local HER2 status, n (%)						
IHC 3+	26 (89.7)	37 (86.0)	35 (85.4)	35 (81.4)	32 (78.0)	26 (81.3)
IHC 2+/ISH+	3 (10.3)	5 (11.6)	5 (12.2)	7 (16.3)	9 (22.0)	6 (18.8)
IHC 2+/ ISH unknown	0	0	0	1 (2.3)	0	0
Missing	0	1 (2.3)	1 (2.4)	0	0	0
Central HER2 status, n (%)						
IHC 3+	18 (62.1)	30 (69.8)	31 (75.6)	30 (69.8)	24 (58.5)	17 (53.1)
IHC 2+/ISH+	1 (3.4)	1 (2.3)	1 (2.4)	4 (9.3)	2 (4.9)	3 (9.4)
IHC 2+/ISH−	1 (3.4)	4 (9.3)	2 (4.9)	1 (2.3)	4 (9.8)	6 (18.8)
IHC 2+/ ISH unknown	1 (3.4)	0	1 (2.4)	0	1 (2.4)	0
IHC 1+	2 (6.9)	1 (2.3)	2 (4.9)	3 (7.0)	3 (7.3)	0
IHC 0	1 (3.4)	2 (4.7)	1 (2.4)	1 (2.3)	5 (12.2)	1 (3.1)
Missing	5 (17.2)	5 (11.6)	3 (7.3)	4 (9.3)	2 (4.9)	5 (15.6)

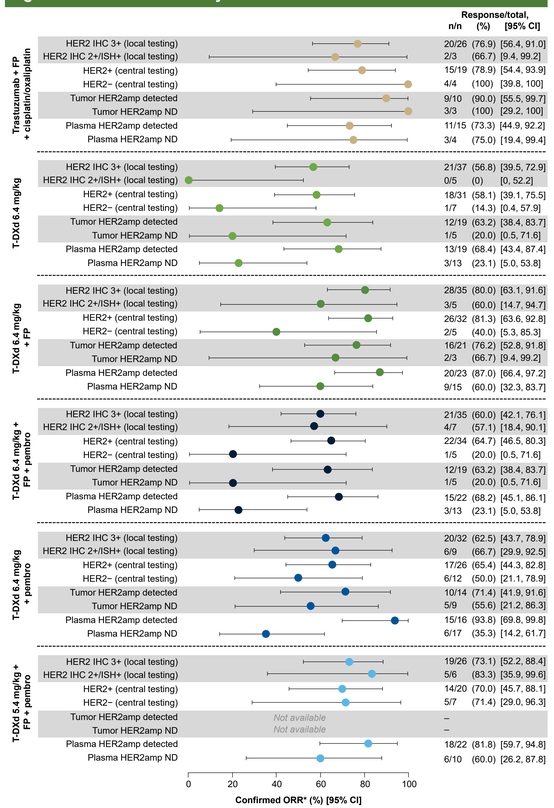
ECOG PS, Eastern Cooperative Oncology Group performance status; FP, fluoropyrimidine; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH(+/−), in situ hybridization(–positive/–negative); pembro, pembrolizumab; T-DXd, trastuzumab deruxtecan

Table 2. Agreement between local and central HER2 IHC results

HER2 status by local testing, n (%)	HER2 status by central testing: IHC 3+	IHC 2+/ISH+	IHC 2+/ISH−	IHC 1+	IHC 0	Total
IHC 3+	134 (80.7)	9 (5.4)	11 (6.6)	4 (2.4)	8 (4.8)	166
IHC 2+/ISH+	14 (42.4)	3 (9.1)	7 (21.2)	7 (21.2)	2 (6.1)	33
Total	148	12	18	11	10	199

Missing/unknown data for n=2 local IHC, n=1 local ISH, n=3 central ISH, and n=24 central IHC results (missing central HER2 IHC results were predominantly due to insufficient tumor content or samples not meeting protocol-defined requirements or being outside of the stability window)
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH(+/−), in situ hybridization(–positive/–negative)

Figure 1. Confirmed ORRs by HER2 status

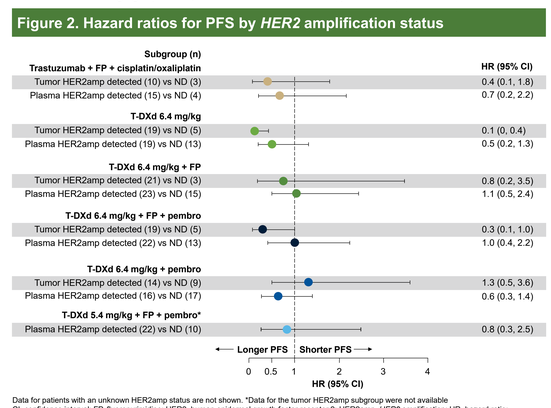


HER2+: HER2 IHC 3+ or IHC 2+/ISH+; HER2−: HER2 IHC 2+/ISH− or IHC 1+/0. Data for patients with unknown HER2 IHC or amplification status are not shown.
*Investigator assessed per RECIST 1.1
CI, confidence interval; FP, fluoropyrimidine; HER2(+/−), human epidermal growth factor receptor 2(−positive/−negative); HER2amp, *HER2* amplification; IHC, immunohistochemistry; ISH(+/−), in situ hybridization(–positive/–negative); ND, not detected; ORR, objective response rate; pembro, pembrolizumab; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan

Efficacy

- Higher investigator-assessed confirmed ORRs were observed for patients with central HER2+ GC, GEJA, or EA versus those with HER2− tumors within treatment arms except in the trastuzumab + FP + cisplatin/oxaliplatin and T-DXd 5.4 mg/kg + FP + pembro arms (**Figure 1**)
  - Investigator-assessed confirmed ORRs were generally higher among patients with baseline tumor or plasma *HER2* amplification compared with those without amplification within treatment arms, respectively, except in the trastuzumab + FP + cisplatin/oxaliplatin arm
- Trends of longer investigator-assessed PFS (hazard ratio ≤0.7) were observed for patients with baseline tumor *HER2* amplification versus those without amplification in the T-DXd 6.4 mg/kg, T-DXd 6.4 mg/kg + FP + pembro, and trastuzumab + FP + cisplatin/oxaliplatin arms (**Figure 2**)
  - Trends of longer investigator-assessed PFS (hazard ratio ≤0.7) were observed for patients with baseline plasma *HER2* amplification versus those without amplification in the T-DXd 6.4 mg/kg, T-DXd 6.4 mg/kg + pembro, and trastuzumab + FP + cisplatin/oxaliplatin arms

Figure 2. Hazard ratios for PFS by *HER2* amplification status



Data for patients with an unknown HER2amp status are not shown. *Data for the tumor HER2amp subgroup were not available
CI, confidence interval; FP, fluoropyrimidine; HER2, human epidermal growth factor receptor 2; HER2amp, *HER2* amplification; HR, hazard ratio; ND, not detected; pembro, pembrolizumab; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

Concordance of *HER2* amplification with central HER2 IHC/ISH status

- PPA of tumor and plasma *HER2* amplification with HER2+ tumors was 96.2% (n=76/79) and 73.1% (n=95/130), respectively; NPA of tumor or plasma *HER2* amplification with HER2− (IHC 2+/ISH−, IHC 1+/0) tumors was 90.9% (n=20/22) and 81.1% (n=30/37), respectively (**Table 3**)

Table 3. Concordance of baseline tissue and plasma *HER2* amplification with central HER2 IHC/ISH status

		HER2 status by central testing: HER2+ IHC 3+	HER2+ IHC 2+ /ISH+	HER2+ IHC 2+ /ISH−	HER2− IHC 1+	HER2− IHC 0	Total
Tumor *HER2* amplification, n (%)	**Detected**	72 (92.3)	4 (5.1)	1 (1.3)	0	1 (1.3)	78
	Not detected	2 (8.7)	1 (4.3)	8 (34.8)	7 (30.4)	5 (21.7)	23
	Total	74	5	9	7	6	101
		PPA 96.2% (n=76/79)		**NPA 90.9% (n=20/22)**			
Plasma *HER2* amplification, n (%)	**Detected**	91 (89.2)	4 (3.9)	5 (4.9)	1 (1.0)	1 (1.0)	102
	Not detected	28 (43.1)	7 (10.8)	13 (20.0)	7 (10.8)	10 (15.4)	65
	Total	119	11	18	8	11	167
		PPA 73.1% (n=95/130)		**NPA 81.1% (n=30/37)**			

Missing/unknown IHC/ISH for seven patients with tumor *HER2* amplification results and 22 patients with plasma *HER2* amplification results
HER2(+/−), human epidermal growth factor receptor 2(−positive/−negative); IHC, immunohistochemistry; ISH(+/−), in situ hybridization(–positive/–negative); NPA, negative percentage agreement; PPA, positive percentage agreement

Limitations

- Interpretation of subgroup analyses were limited by sample sizes within treatment arms
- Collection of patient tissue and plasma samples was not time matched

Acknowledgments

Under the guidance of the authors and in accordance with Good Publication Practice (GPP) guidelines, medical writing and editorial support was provided by Samuel Shields, PhD, of Helios Medical Communications, part of the Helios Global Group, and was funded by AstraZeneca.

Disclosures

Dr Yelena Y Janjigian reports stock options with Inspirna, OncoDaily, and Veeda Oncology; honoraria from AbbVie, AmerisourceBergen, Arcus Biosciences, AskGene Pharma Inc., Astellas, AstraZeneca, Basilea Pharmaceutica, Bayer, BeOne Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Clinical Care Options, Daiichi Sankyo, eChinaHealth, Eisai Co., Ltd., Eli Lilly, Geneos Therapeutics, Gilead Sciences, GlaxoSmithKline, Guardant Health, H.C. Wainwright & Co., HMP Education, i3 Health, IDEOlogy Health, Imedex, Imugene, Inspirna, Lynx Health, Master Clinician Alliance, Merck, Merck Serono, Mersana Therapeutics, Michael J. Hennessy Associates, Oncology Information Group, Paradigm, PeerView Institute, Pfizer, Physicians' Education Resource®, LLC, Regeneron, Research to Practice, Sanofi, Seagen, Silverback Therapeutics, Suzhou Liangyihui Network Technology Co., Ltd., Talem Health, TotalCME, WebMD, LLC, and Zymeworks Inc.; consulting or participation on an advisory board with AbbVie, AmerisourceBergen, Arcus Biosciences, AskGene Pharma Inc., Astellas, AstraZeneca, Basilea Pharmaceutica, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Clinical Care Options, Daiichi Sankyo, Debbie's Dream Foundation, Eisai Co., Ltd., Eli Lilly, Geneos Therapeutics, GlaxoSmithKline, Guardant Health, H.C. Wainwright & Co., HMP Education, Imedex, Imugene, Inspirna, Jazz Pharmaceuticals, Lynx Health, Merck, Merck Serono, Mersana Therapeutics, Michael J. Hennessy Associates, OncLive, OncoDaily, Paradigm Medical Communications, PeerView Institute, Pfizer, Physicians' Education Resource®, LLC, Research to Practice, Sanofi, Seagen, Signatera, Silverback Therapeutics, WebMD, LLC, and Zymeworks Inc.; research funding from Arcus Biosciences, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Cycle for Survival, Eli Lilly, Fred's Team, Genentech/Roche, Inspirna, Merck, National Cancer Institute, Stand Up To Cancer, Transcenta, and the U.S. Department of Defense; travel, accommodation, and expenses with Bristol Myers Squibb and Merck; and other relationships with Axis Medical Education, Clinical Care Options, Giants of Cancer Care, and Research to Practice

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